GUIDELINES FOR REVIEW OF CLINICAL RESEARCH TRIAL APPLICATIONS

National Institutes of Diabetes and Digestive and Kidney Diseases

A clinical research trial grant or contract is intended to support clinical evaluation of various methods of therapy or treatment in specific disease areas. These are usually collaborative programs between sponsoring institutions and key investigators in participating clinical research hospitals. Thus, a sufficiently large patient population becomes available for study to enable the investigation to come to fruition within a reasonable period of time. This document provides guidelines for preparation and review of such applications with specific reference to the necessary components of such a collaborative relationship and the standards by which these components should be assessed.

A "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention of comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacological, non-pharmacological, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included. (NIH Guide, v.23, n.11; 3/18/94)

EVALUATION OF APPLICATIONS

PRIMARY AND SECONDARY REVIEWERS should provide an overall evaluation, briefly summarizing the most important points of your critique, weighting the review criteria as you feel appropriate, and evaluating the overall impact of the research on the field. (Note: an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high merit rating.) In the critique, the five review criteria should be addressed as separate sections. If this is a competing continuation application, evaluate the progress made during the previous funding period either as a separate paragraph or under the individual criteria as appropriate. If this is an amended application, address progress, changes, and responses to the critique from the previous review, indicating whether the application is improved, the same as, or worse than the previous submission. However, you are not constrained to address only the points identified in the previous review. These comments on progress and responsiveness to previous critiques should be provided either in a separate paragraph and/or under the appropriate criteria.

DISCUSSANTS The written critique for a discussant review may be brief; all aspects of the five review criteria do not need to be specifically addressed. A brief paragraph highlighting the strengths and weaknesses of the application (essentially equivalent to an overall evaluation section) or bulleted lists of strengths and weaknesses are both examples of acceptable critiques. If you prefer to prepare a full critique equivalent to a primary or secondary review, you also have that option.

CRITERIA FACTORED INTO PRIORITY SCORE

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Approach: Are the conceptual or clinical framework, design (including the composition of the study population), methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

In addition, consider these aspects of the study design in your comments:

- Feasibility and likelihood of achieving the objectives of the clinical trial, including ability to recruit, retain, and follow subjects

- Evidence of pilot phase experience and patient accession.

For coordinating center activities, consider the following issues:

- Specific competence and experience of the professional and technical staff pertinent to clinical trial coordination, data management and quality control, and statistical analysis functions (assess the time and effort to be devoted for appropriateness to the trial)
- Adequacy of the proposed facility, including technical hardware and space
- Adequacy of organizational and administrative structure for the proposed project and of systematic planning for the design of operations
- Merit of the statistical features of the study, including such characteristics as sample size projections, statistical power, methods of analyses, and sequential analyses of data where indicated

For participating institutions such as clinical centers, which will take part in the trial but will not have coordinating functions, consider the following aspects:

- Qualifications and experience of the investigators
- Availability of technical resources
- Appropriateness of internal organization and administration
- Commitment of the institution and relevant staff
- Availability of patients, including the ability to recruit and retain appropriate subjects
- Commitment to following joint protocols and furnishing data in a timely and accurate manner;
- Actual or proposed commitment to cooperate with other participating hospitals and the coordinating center

For competing renewals, evaluate progress, recruitment, publications, findings, and cooperative activities to date.

Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

Investigators: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)? Do not include descriptive biographical information.

Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support? Do not describe available facilities and equipment.

Human Subjects: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398). If exemptions are claimed, express any comments or concerns about the appropriateness of the exemption(s) claimed. If no exemptions are claimed, express any comments or concerns about the appropriateness of the responses to the four required points, especially whether the risks to subjects are reasonable in relation to the anticipated benefits to the subjects and in relation to the importance of the knowledge that may reasonably be expected to result from the research.

Data and Safety Monitoring Plan: Evaluate the Data and Safety Monitoring plan provided by the applicant. As of the October 2000 receipt date, the NIH requires that all applicants must supply a general description of the Data and Safety Monitoring Plan for all Phase I, II, and III clinical trials as part of the research application. In addition, Phase III clinical trials require a Data Safety Monitoring Board. The principles of data and safety monitoring require that all biomedical and behavioral clinical trials be monitored to ensure the safe and effective conduct of human subjects research, and to recommend

conclusion of the trial when significant benefits or risks are identified or if it is unlikely that the trial can be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the methods and degree of monitoring should be commensurate with risk. Please refer to the "NIH INSTRUCTIONS TO REVIEWERS FOR EVALUATING RESEARCH INVOLVING HUMAN SUBJECTS IN GRANT AND COOPERATIVE AGREEMENT APPLICATIONS- APRIL 5, 2002" for more information. This document is available on the enclosed CD and at the following website: http://grants1.nih.gov/grants/peer/hs_review_inst.pdf.

Also please refer to the NIDDK web site for additional information at: http://www.niddk.nih.gov/patient/patient.htm#policy

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children (individuals under 21 years of age) as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398). In conformance with NIH policy, the use of women, children, and minority individuals in patient populations is an issue that should be addressed in any application which involves clinical research.

For more information, see (http://grants.nih.gov/grants/guide/notice-files/not98-024.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html.

Clinical research includes "...human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials". If there is no compelling rationale provided for the exclusion or under-representation of women, children, and minorities from the patient study population, this constitutes a flaw in experimental design and should be reflected in the priority score. Reviewers are asked to inform the Scientific Review Administrator if such concerns exist and to comment specifically on these issues in their critiques. In addition, you will be asked to recommend a code for the application, using categories 1 to 4 as follows. Also determine whether the research is a Phase III clinical trial.

CODE	Minority (M)	Gender (G)	Children (C)
1	minority and non-minority	both females and males	both children and adults
2	only minority	females only	children only
3	only non-minority	males only	no children included
4	representation unknown	unknown	unknown

Evaluate acceptability as "A" (acceptable) or "U" (unacceptable). If you rate the sample as "U", consider this feature a weakness or a deficiency in the design of the project reflected in the overall scoring of the application. NOTE: To the degree that acceptability or unacceptability impacts on the investigator's approach to the proposed research, such comments should also appear under Approach in the five major review criteria above and should be factored into the score as appropriate.

OTHER CONSIDERATIONS

Budget: Evaluate direct costs only. For all years, determine whether all items of the budget are appropriate and justified. Provide a rationale for each recommended modification in amount and/or duration of support. With regard to personnel, do not be concerned with the salary requested but with the percent effort proposed. The priority score should not be affected by the evaluation of the budget.

Scientific/Budgetary Overlap: If it is identified in an application, it should be noted in a statement separate from the critique and should not be considered in the evaluation of the application. Identify of there is an overlap of aims or excessive effort between this application and other active or pending support. Reviewers are asked to focus on the scientific and technical merit of the application. The Scientific Review Administrator will ensure that such issues are documented in the summary statement as an administrative note. Purported overlap must be resolved by NIH staff before an award is made.

Model Organism Sharing Plan: All NIH applications (regardless of budget) where the development of model organisms is anticipated are to include a description of a specific plan for sharing and distributing unique model organism research resources or state appropriate reasons why such sharing is restricted or not possible. Please comment on the adequacy of the sharing plan, taking into consideration the organism, the timeline, and the applicant's decision to distribute the resource or deposit it in a repository. Your assessment of the sharing plan should not be factored into the priority score of the application. Your comments will be captured in an administrative note.

Data Sharing Plan: Investigators seeking $500,000 or more in direct costs in any year must include a brief one-paragraph description of how final research data will be shared, or explain why data sharing is not possible. Applicants are encouraged to discuss their data sharing plan with their program contact at the time they negotiate an agreement with the Institute/Center (IC) staff to accept assignment of their application. http://grants.nih.gov/grants/policy/data_sharing/index.htm. Please comment on the adequacy of the sharing plan. Your assessment of the sharing plan should not be factored into the priority score of the application; your comments will be captured in an administrative note.

Biohazards: If biohazardous materials are to be used in the proposed research, the Principal Investigator should address the proper handling of such items. Note any materials or procedures that are potentially hazardous to research personnel and indicate whether the protection proposed will be adequate.

Foreign Institutions: If the applicant organization is foreign, comment on any special talents, resources, populations, or environmental conditions that are not readily available in the United States or that provide augmentation of existing U.S. resources. In addition, indicate whether similar research is being performed in the U.S. and whether there is a need for such additional research. These aspects do not apply to applications from U.S. organizations for projects containing a significant foreign component.

10/06